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Clinical applications of intravenous immunoglobulins (IVIg) – beyond immunodeficiencies and neurology

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Summary

The clinical use of intravenous immunoglobulin (IVIg) has expanded beyond its traditional place in the treatment of patients with primary immunodeficiencies. Due to its multiple anti-inflammatory and immunomodulatory properties, IVIg is used successfully in a wide range of autoimmune and inflammatory conditions. Recognized autoimmune indications include idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, Guillain–Barré syndrome and other autoimmune neuropathies, myasthenia gravis, dermatomyositis and several rare diseases. Several other indications are currently under investigation and require additional studies to establish firmly the benefit of IVIg treatment. Increasing attention is being turned to the use of IVIg in combination with other agents, such as immunosuppressive agents or monoclonal antibodies. For example, recent studies suggest that combination therapy with IVIg and rituximab (an anti-CD20 monoclonal antibody) may be effective for treatment of autoimmune mucocutaneous blistering diseases (AMBDs), with sustained clinical remission. The combination of IVIg and rituximab has also been used in the setting of organ transplantation. Firstly, IVIg ± rituximab has been administered to highly human leucocyte antigen (HLA)-sensitized patients to reduce anti-HLA antibody levels, thereby allowing transplantation in these patients. Secondly, IVIg in combination with rituximab is effective in the treatment of antibody-mediated rejection following transplantation. Treatment with polyclonal IVIg is a promising adjunctive therapy for severe sepsis and septic shock, but its use remains controversial and further study is needed before it can be recommended routinely. This review covers new developments in these fields and highlights the broad range of potential therapeutic areas in which IVIg may have a clinical impact.

Keywords: autoimmunity, immunoglobulin, vasculitis, sepsis, transplantation

Introduction

Intravenous immunoglobulins (IVIgs) are therapeutic preparations of pooled polyspecific IgG obtained from the plasma of a large number of healthy individuals. These preparations were commercialized in the early 1980s to replace intramuscular preparations of polyspecific IgG, which were the only available substitutive therapy at that time for patients with primary or secondary immunodeficiencies. For patients with primary immunodeficiencies, IVIg (or subcutaneous immunoglobulin – SCIg) remains the treatment option of choice.

In 1981, Imbach and colleagues reported that, in patients with Wiskott–Aldrich syndrome who presented with thrombocytopenia and hypogammaglobulinaemia, high-dose IVIg infusion was followed by an increase in the platelet count [1]. Since then, IVIg has been demonstrated to be effective in idiopathic thrombocytopenic purpura (ITP) and a large number of autoimmune and/or systemic inflammatory diseases, notably Kawasaki disease, and in immune-mediated neurological disorders such as Guillain–Barré syndrome (GBS), chronic idiopathic demyelinating polyneuropathy (CIDP), multi-focal neuropathy with conduction block (MNCB) and acute myasthenia gravis [2].

For other diseases, IVIg is not always used as a first-line therapy. It may be administered as a steroid-sparing agent and in certain conditions may represent an alternative to other available therapeutic approaches, such as immunosuppressants, plasma exchange or monoclonal antibodies. IVIg is also often employed to treat diseases that are refractory to other treatments or where conventional therapies result in unacceptable side effects. Combination therapy of IVIg with immunosuppressants has been applied successfully in several conditions, including autoimmune vasculitis, dermato- and polymyositis, transplantation and sepsis [2].

When considering the emerging uses of IVIg, it is important to consider the evidence base. In some patient populations the therapeutic value of IVIg has been proven in large controlled trials, while in other patient populations only small, uncontrolled studies or case reports are available, often due to the small numbers of patients with these rare diseases.

IVIg for the treatment of autoimmune and inflammatory disorders

Despite the large number of autoimmune diseases being treated with IVIg, guidance on the clinical usage is limited to only three conditions: ITP, GBS and Kawasaki disease. Because of the costs, finite supply and time for the patient receiving IVIg therapy, there is a need to rationalize and prioritize the disorders for which, based on currently available evidence, IVIg is adopted. In France, the Comité d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT) IVIg expert group, chaired by Professor Loïc Guillevin, aims to identify scientifically validated uses and issue recommendations regarding the usage of IVIg [3]. Guidelines for the use of immunoglobulin have also been developed in the United Kingdom [4], Canada [5,6], Australia [7] and elsewhere.

Indications have been divided into those patients for whom the benefit of IVIg treatment is recognized, those under evaluation and those where benefit is not documented. Recognized indications include ITP, Kawasaki disease, myasthenia gravis, dermatomyositis (DM), as well as autoimmune neuropathies such as GBS, chronic inflammatory demyelinating polyradiculoneuropathy, multi-focal motor neuropathy (MMN) and stiff person syndrome. IVIg efficacy is also recognized in rare diseases, such as parvovirus B19 infection, autoimmune erythroblastopenia and neutropenia, acquired hypocoagulability and birdshot retinochoroidopathy; however, no prospective randomized studies in these indications exist, due mainly to the rarity of these conditions.

Indications that are currently under evaluation by CEDIT include inclusion body myositis (IBM), demyelinating central nervous system diseases (but not multiple sclerosis or Devic syndrome), corticoresistant polymyositis, autoimmune encephalitis and refractory epilepsy. The efficacy of IVIg in the treatment of select populations of transplant patients, haemolytic anaemia, adult-onset Still's disease, anti-phospholipid syndrome, anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitides and pemphigus vulgaris is also under evaluation.

IVIg for the treatment of autoimmune vasculitides

Systemic vasculitides are classified based on the diameter of the vessels involved. Large vessel involvement is found in giant cell arteritis and Takayasu's arteritis, while medium vessels are affected in diseases such as polyarteritis nodosa and Kawasaki disease. Small vessels are involved in necrotizing glomerulonephritis and ANCA-associated systemic vasculitides.

Kawasaki disease is characterized by a systemic inflammation of the blood vessels and affects predominantly children under the age of 5 years [8]. It is one of the first vasculitides reported to be treated with IVIg, with or without acetyl salicylic acid (aspirin) [9,10]. Since then, IVIg in combination with aspirin has become the standard of care for patients with Kawasaki disease [11]. A meta-analysis of 16 prospective randomized trials was conducted in 2003, showing that there is a significant decrease in new coronary abnormalities at day 30 in patients treated with IVIg compared with placebo and demonstrated that infusion of a single dose of 2 g/kg body weight induces a significant reduction in coronary aneurysms at day 30 [8]. The analysis concluded that children fulfilling the diagnostic criteria for Kawasaki disease should be treated with 2 g/kg of IVIg within 10 days of the first symptoms in order to gain the maximum benefit [8].

Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg–Strauss syndrome (CSS) are small-sized vessel vasculitides that are associated frequently with anti-neutrophil cytoplasmic autoantibodies [12]. ANCA-associated vasculitides are characterized by vascular necrosis either in the glomerular visceral epithelial cells or in other visceral tissues. Renal and lung involvement is often observed. The major target of anti-neutrophil antibodies in WG is proteinase 3, whereas in MPA and CSS the antibodies target myeloperoxidase (MPO). Treatment of ANCA-associated vasculitides is initiated commonly with induction therapy of corticosteroids, cyclophosphamide and sometimes plasma exchanges. Maintenance therapy usually involves azathioprine, methotrexate or mycophenolate mofetil (MMF). Relapses of ANCA-associated vasculitides are often treated with immunosuppressants, such as cyclophosphamide or methotrexate or with biologicals such as IVIg, anti-TNF or anti-CD20 therapy. Plasma exchanges can also be used in this setting.

Several small prospective clinical studies of IVIg treatment of ANCA-associated vasculitides have been conducted (Table 1). The first open prospective study of seven patients with WG, MPA or rheumatoid vasculitis was performed in

Table 1. Clinical studies of the use of intravenous immunoglobulin (IVIg) for the treatment of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis.

First author, year	Study design	Patients included (*n*)	Previous treatment	Response to treatment
Jayne, 1991 [13]	Open, prospective	7 (3 WG, 3 MPA, 1 RA-vasculitis)	5 TR, 2 first-line	6 CR 1 transient response
Jayne, 1993 [14]	Open, prospective	26 (14 WG, 11 MPA, 1 RA-vasculitis)	17 TR, 9 first-line	13 CR, 13 PR 6 relapses at 1 year
Richter, 1995 [15]	Open, prospective	15 (14 WG, 1 MPA)	14 TR, 1 first-line	6 PR 9 failures
Jayne, 1996 [83]	Open, prospective	6 (3WG, 3 MPA)	6 first-line	4 CR 2 relapses
Levy, 1999 [16]	Open, prospective	10	10 TR	6 CR or PR
Jayne, 2000 [17]	Randomized, placebo controlled	34	IVIg	14/17 improved (IVIg) 6/17 improved (placebo)
Martinez, 2008 [18]	Open, prospective	22 (19 WG, 3 MPA)	Corticosteroids or immunosuppressants	13 CR, 1 PR, 7 relapses, 1 failure

CR: complete response; MPA: microscopic polyangiitis; PR: partial response; RA: rheumatoid arthritis; TR: 'resistant to treatment with cyclophosphamide and prednisone'; WG: Wegener's granulomatosis.

1991 and showed promising results, with six patients in complete remission and one with transient response to IVIg therapy (total dose 2 g/kg) [13]. This study was followed by an extensive report on 26 patients, showing that 8 weeks after IVIg treatment 13 patients were in full and 13 in partial remission [14]. The clinical benefit was maintained in 18 patients for up to 1 year after IVIg therapy. Conflicting results were obtained in another study of 15 patients with ANCA-associated vasculitis who responded poorly to conventional therapy. These patients were treated with single or multiple courses of IVIg, to a total dose of 30 g/day over 5 days [15]. Six of 15 patients experienced significant clinical benefit; however, no patient experienced complete remission. Another study with patients resistant to conventional treatment similarly showed that IVIg treatment was effective in six of 10 patients [16]. Only one randomized, placebo-controlled trial of IVIg in ANCA-associated vasculitis has been conducted to date (Table 1). The study investigated the efficacy of a single course of IVIg (total dose 2 g/kg) in previously treated patients with persistent disease. At the 3-month time-point (primary end-point), 14 of 17 patients showed improvement in response to IVIg treatment, compared with six of 17 in the placebo group ($P = 0{\cdot}035$). However, this was a short trial of only 3 months, so there is still need for additional data in this setting [17].

A recent open, prospective non-randomized study evaluated the efficacy and safety of IVIg administered for 6 months for the treatment of relapses of WG, MPA or CSS that occurred during or within 1 year following the withdrawal of corticosteroids and/or immunosuppressants (Table 1) [18]. The study evaluated 22 patients (21 with ANCA-specific antibodies). Twenty-one patients experienced partial initial responses and, at 9 months, 13 patients experienced complete remission. At 24 months, eight patients were in complete remission in the absence of any other treatment, while another 10 were in remission with the help of treatment modification.

Although studies in a number of ANCA-associated vasculitides have shown some benefit of IVIg treatment, proven efficacy is observed in only a handful of conditions. For example, the benefits of IVIg in the treatment of Kawasaki disease are well documented, and the data suggest that children meeting the diagnostic criteria for this disease must be treated within 10 days of the onset of symptoms. IVIg may also represent an option in patients with relapsing ANCA-associated vasculitides, but additional randomized controlled trials are needed in this field.

Combination therapy with IVIg in autoimmune mucocutaneous blistering diseases

Autoimmune mucocutaneous blistering diseases (AMBDs) are rare but potentially fatal diseases. Since the introduction of corticosteroids, the annual mortality rate due to blistering diseases has fallen; nonetheless patients suffering from these conditions continue to experience high morbidity and mortality.

There are currently two approaches to the pharmacological management of AMBDs. One approach targets the production of the autoantibody in the bone marrow, spleen and lymph nodes, and involves the use of immunosuppressive drugs such as azathioprine, MMF, cyclophosphamide and methotrexate. The other approach targets the sites at which the autoantibodies exert their effects, namely in the skin or mucosal surfaces. This approach uses anti-inflammatory drugs, such as prednisone and dapsone, to ameliorate the effects of the autoantibodies [19].

Conventional immunosuppressive therapy for the treatment of AMBDs involves high-dose corticosteroids (80–240 mg/day) for prolonged periods of time. However,

this therapy is not always effective and usually results in a poor quality of life. Conventional immunosuppression has a variety of reversible and non-reversible side effects, including prolonged vulnerability to infection and increased risk of cancer. Indeed, the side effects of such therapies are often the ultimate cause of death in these patients.

IVIg is usually employed when conventional therapy fails, causes side effects or is contraindicated. Beneficial clinical effects of IVIg have been demonstrated in the treatment of a number of AMBDs, including pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid and epidermolysis bullosa aquisita (EBA). A 'Consensus Statement' on the use of IVIg in these diseases recommends a dose of 2 g/kg/cycle, given monthly until clinical control, with a progressive increase of the intervals between the cycles thereafter to 6, 8, 10, 12 and 14 weeks [20]. The last cycle is given after a 16-week interval, and is considered as the end of therapy.

In a recent study, 156 patients with AMBD treated with IVIg using this protocol demonstrated successful clinical outcomes [21]. In these patients IVIg could be used as monotherapy, once concomitant prednisone and immunosuppressive agents were gradually discontinued. These included 42 patients with pemphigus vulgaris, 26 with pemphigus foliaceus, 32 with bullous pemphigoid, 68 with mucous membrane (cicatricial) pemphigoid and nine with epidermolysis bullosa acquisita. IVIg produced long-term, sustained remission for at least 2 years of follow-up, after discontinuing IVIg therapy. The patients were in serological remission and enjoyed a high quality of life. It could be speculated that, compared to previous therapies, IVIg changed the clinical course of these diseases [21].

As a therapeutic option, the costs associated with IVIg use are often perceived to be high. However, when the true costs of conventional therapy are calculated, including the costs of the treatment of side effects and hospitalizations, they are approximately two- to threefold higher than the costs of IVIg therapy. According to one US analysis, the true cost of conventional therapy for pemphigus vulgaris was $US 123 133 per patient per year, while the mean annual cost of IVIg was $US 76 249 [22].

A large study analysed 275 patients who had been treated according to the Consensus Statement protocol and who remained in clinical remission for a minimum of 2 years after discontinuing IVIg (unpublished data). About 70% of the patients responded to IVIg monotherapy and were considered high responders. The remaining 30% were partial responders or non-responders. Partial responders, in whom the dose of prednisone and immunosuppressive agent was reduced by 50% or less, were subclassified as mild (clinical response of 50% or less) or moderate (clinical response between 50% and 100%) responders. Moderate responders were treated subsequently with 50–150 mg dapsone daily. Clinical improvement was achieved in less than 4 months (mean 3·8, range 2·1–7·5). Mild responders were treated with oral methotrexate (5–20 mg/weekly) and dapsone (50–150 mg daily). These patients responded to therapy within 6 months (mean 5·7, range 4–8·6). Thereafter, the clinical response of each group of patients was the same as that observed in the high responder group. Non-responders were patients whose disease, in spite of adjunctive therapy, flared if the interval between cycles was increased by more than 4 weeks, or who continued to have active disease after 1 year of IVIg therapy. These patients were treated with rituximab and IVIg, and all showed clinical improvement.

Table 2. Results of therapy with intravenous immunoglobulin (IVIg) and rituximab in patients with pemphigus vulgaris [23].

Variable	Value
Time to first improvement	
No. of patients	11
Median – weeks (range)	4 (3–6)
Time to complete remission	
No. of patients	9
Median – weeks (range)	9 (7–9)
Duration of complete remission	
No. of patients	9
Median – months (range)	31 (22–37)
Recurrence	
No. of patients	2
Time to first recurrence – months	
Patient 10	12
Patient 11	12
Duration of most recent remission – months	
Patient 10	24
Patient 11	15

It has been demonstrated previously that the combination of IVIg and rituximab is effective in patients with refractory pemphigus vulgaris who had inadequate responses to conventional therapy and IVIg. Patients were treated with two cycles of rituximab (375 mg/m^2 of body-surface area) once weekly for 3 weeks and IVIg (2 g/kg) in the fourth week, followed by a monthly infusion of rituximab and IVIg for 4 months [23]. In this study, nine of 11 patients showed rapid resolution of lesions and a clinical remission lasting 22–37 months (mean 31·1 months) (Table 2). All immunosuppressive therapy, including prednisone, could be discontinued. Two patients were treated with rituximab only during recurrences and had sustained remission. None of the patients in this study had serious side effects, although the long-term consequences of rituximab and IVIg combination therapy in such patients with autoimmune diseases are unknown and need to be investigated.

These studies suggest that combination therapy with IVIg may be effective for treatment of AMBDs. Rituximab can convert partial responders to high responders and these patients, once in remission, maintain a sustained prolonged clinical remission.

Transplantation and IVIg therapy

Modern immunosuppressive regimens have greatly improved the outcomes of the majority of patients after transplantation. The development of new approaches, including the use of IVIg and rituximab, has provided hope for a select group of transplant patients for whom prognosis was previously poor, namely 'highly sensitized' patients.

Sensitization occurs when individuals are exposed to human leucocyte antigens (HLA) that are different from their own. This can happen through blood transfusion, previous transplantation or pregnancies [24]. Sensitization is of little consequence unless that person requires a transplant. Patients with high levels of preformed anti-HLA antibodies (panel-reactive antibodies; PRA) who receive a transplant are at increased risk for acute rejection episodes, and have poorer graft survival [25]. As a consequence, the cost of care for sensitized patients in the first year after transplantation is higher than for non-sensitized patients, and patients are more likely to return to dialysis [26]. Hence, such patients often spend more time on the waiting list or do not receive a transplant.

In highly HLA-sensitized cardiac and renal allograft recipients, a high-dose IVIg protocol has been shown to reduce allosensitization, ischaemia–reperfusion injuries and acute rejection episodes, and to improve long-term allograft outcomes [27,28]. In a multi-centre study comparing IVIg treatment with placebo, IVIg was superior to placebo in lowering anti-HLA antibody levels ($P = 0{\cdot}004$) and increased the rates of transplantation from 17% to 35% [29]. The predicted mean time to transplantation was 4·8 years in the IVIg group *versus* 10·3 years in the placebo group ($P = 0{\cdot}02$), demonstrating that IVIg can offer significant benefits in highly HLA-sensitized patients.

Critical to the success of these desensitization protocols is the monitoring of antibody levels to assess efficacy of treatment, both pre- and post-transplantation. Acceptable levels of donor specific antibody (DSA) that allow for successful desensitization must be determined, as well as post-desensitization DSA levels that allow for successful transplantation and long-term graft function. Zachary and colleagues have shown that the initial titre and specificity of the DSA are critical in determining the likelihood of successful desensitization [30]. Quantitative solid-phase antibody methodologies provide a defined approach to monitor the feasibility and efficacy of the desensitization protocols. In a study of pre- and post-transplant sera from 16 patients with DSA before desensitization, the DSA strength was quantified by single antigen Luminex bead assay (expressed as standard fluorescence intensity; SFI) [31]. Patients with DSA $> 10^5$ and T cell flow cross-match results > 200 mean channel shifts (MCS) were found to be at higher risk for antibody-mediated rejection. After treatment of the rejection, serum creatinine levels improved without significant changes in DSA. This technique may be useful to identify patients at higher risk for rejection, and to monitor changes in a post-transplant antibody course.

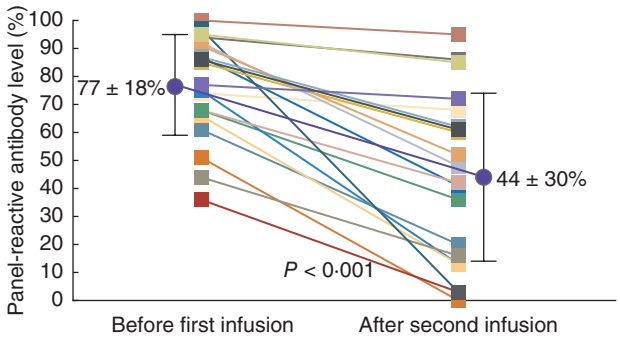

Fig. 1. Panel-reactive antibody titres pre- and post-intravenous immunoglobulin (IVIg) plus rituximab treatment. Individual data from the 20 study patients before the first infusion of IVIg and after the second infusion are shown. The pretreatment and post-treatment means are also shown, as determined with the T cell complement-dependent cytotoxicity panel-reactive antibody assay. The means were significantly different ($P < 0{\cdot}001$). Error bars denote standard deviations. Reproduced with permission from Vo *et al.* 2008 [5].

Rituximab, a chimeric anti-CD20 monoclonal antibody, has shown efficacy in the treatment of antibody-mediated rejection (AMR) [23,32–34]. A recent study described a beneficial effect of the combination of IVIg + rituximab in 20 highly sensitized patients [35]. In this protocol, 2 g/kg IVIg was delivered on week 0, followed by 1 g rituximab on weeks 3 and 4 and a second dose of IVIg on week 5. Following this desensitization therapy, PRA levels were reduced significantly (from 77 ± 19% before first infusion to 44 ± 30% after the second infusion) (Fig. 1). Transplantation was possible in 16 of the 20 patients in the study, and 12-month patient and allograft survival rates were 100% and 94%, respectively. Serum creatinine levels, as a marker of kidney function, were normal in most patients, except for one who lost the graft. No infections or progressive multi-focal leucoencephalopathy were observed.

Because one dose of rituximab was sufficient to suppress B cell responses, an adapted desensitization protocol, with only one dose of rituximab delivered at week 4, has been used recently to treat 113 patients with HLA mismatches who later received a kidney transplant. Mean flow cytometric mismatching was reduced significantly using this regimen. The 2-year patient and graft survival rates were 98% and 93%, respectively (Fig. 2). Twenty-one patients (19%) experienced AMR, and seven of those lost their graft to AMR. Apart from those patients who lost their grafts, all have had excellent outcomes, with good serum creatinine levels.

In conclusion, these advances have enabled patients considered previously to be poor or unreasonable candidates for transplantation to receive a successful transplant. Alternative approaches to IVIg/rituximab-based desensitization include the addition of plasmapheresis and possible splenectomy.

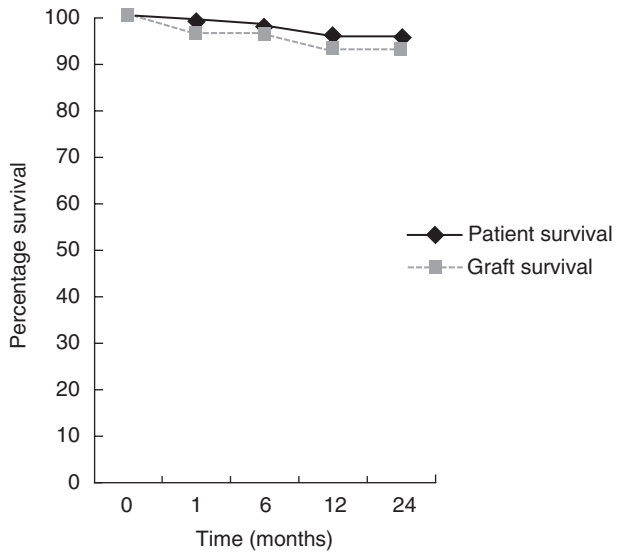

Fig. 2. Patient and graft survival 2 years post-transplant for 113 highly-sensitized dialysis patients transplanted after desensitization with intravenous immunoglobulin (IVIg) plus rituximab. Patient and graft survival rates were 98% and 93%, respectively.

New advances in detecting DSA cellular effectors that mediate AMR and assessment of antibody-mediated injury to allografts (C4d staining) allow for early detection of AMR and early implementation of plasmapheresis, IVIg/rituximab and other therapies to prevent allograft loss.

IVIg for the treatment of sepsis and the systemic inflammatory response syndrome in adults

Severe sepsis and septic shock are clinical conditions characterized by systemic inflammation associated with serious infection. Systemic inflammatory response syndrome (SIRS) is defined most often as the presence of two or more of the following: abnormal temperature (> 38°C or < 36°C); tachycardia (> 90 per min); tachypnoea (> 20 per min); or changes in white blood cell count (< 4000 or > 12 000 cells/μl or > 10% band forms) [36]. Severe sepsis is defined by SIRS due to infection associated with organ dysfunction, hypoperfusion or hypotension. Patients with severe sepsis criteria and persistent hypotension, despite adequate fluid volume replacement, are classified as having septic shock.

Severe sepsis and septic shock are major causes of short- and long-term morbidity and mortality in critically ill adults [37–39]. Severe sepsis and septic shock occur at an incidence of approximately 75–150 per 100 000 people in developed countries [37,40–43]. There is also evidence to support that these rates have increased over the past decades, although it is less well defined as to whether this has been the case since the turn of the new millennium [37,40,44]. Case-fatality rates are among the highest observed of any other acute illness, with severe sepsis and septic shock resulting in death in approximately 30% and 50% of cases, respectively [39,41–46].

Development of novel agents and improvement of existing therapies for severe sepsis and septic shock have been a major area of active laboratory and clinical research during recent decades. Research into the use of adjunctive non-steroidal anti-inflammatory agents, high-dose corticosteroids and biotherapeutic agents in the 1980s and 1990s led to disappointing results [47–51]. However, since 2000 there have been several publications of clinical trials demonstrating major improvements in mortality outcome in critically ill adults with severe sepsis and septic shock [52–56]. This led to concerted efforts among a number of organizations to reduce sepsis mortality. One such effort, the Surviving Sepsis Campaign, aimed to reduce sepsis mortality by 25% by 2009. A number of guidelines were developed with recommendations for early aggressive resuscitation, prompt anti-microbial therapy, use of low-dose corticosteroid therapy, intensive insulin, vasopressin infusion, intensive dialysis and activated protein C infusion, and other clinical scenarios [57]. However, subsequent studies have either cast doubt on or excluded a significant treatment effect of many of these measures [58–61] and have prompted either further clinical trials or downgrading of recommendations [62].

Although antibody therapies were important in the past, they have often been neglected as a potential treatment in recent years. Serum therapies were developed prior to the anti-microbial era and had evident clinical efficacy [63,64]. However, they were largely abandoned once antibiotics became widely available due to their lower efficacy and high incidence of reactions, such as serum sickness. When highly purified human plasma-derived polyclonal IVIgs were developed, they presented a potential for therapy for severe infections. IVIgs have broad and potent activity against micro-organisms and their extracellular products, potent immunomodulatory effects and a well-documented safety profile [65]. However, in part because of uncertainty of benefit, cost and limitations in supply, IVIg has not been adopted widely into clinical practice.

Numerous clinical trials evaluating IVIg adjunctive therapy for sepsis in adults have been conducted over recent decades and have been the subject of multiple meta-analyses, as shown in Table 3 [66–71]. Alejandria and colleagues reported a Cochrane review of 11 trials comparing IVIg with placebo or standard therapy and found a significant mortality reduction [66]. This report was limited by failure to include a number of relevant studies and was improved upon by a subsequent meta-analysis by Pildal and Gotzsche [67]. These authors included 21 trials and similarly found a significantly improved mortality outcome overall with the use of IVIg (Table 3). However, due in part to the inclusion of a high-quality study of 624 patients reported at that time in abstract format only [72], no significant benefit was observed among a prespecified subgroup analysis of high-quality studies [relative risk 1·02 (95% confidence interval,

Table 3. Meta-analyses of randomized clinical trials of intravenous immunoglobulin (IVIg) for treatment of severe sepsis and septic shock.

First author, year	Population	No. of studies included	No. of patients (*n*)	RR for mortality with IVIg (95% CI)	Conclusions
Alejandria, 2002 [66]	BS, SSH	11 (5 PD)	492	0·64 (0·51–0·80)	Reduces mortality; small studies of low quality, insufficient data to recommend
Pildal, 2004 [67]	SE, SSH	21 (7 PD)	1711	0·77 (0·68–0·88)	IVIg use reserve for further clinical trials
Neilson, 2005 [68]	Adults with SS, SSH; treated with IgMA-enriched IVIg	9	435	0·57 (0·43–0·74)	IgMA-enriched IVIg is clinically effective but further study needed
Turgeon, 2007 [69]	Adults with SE, SS or SSH	18 (20 publications)	2569	0·74 (0·62–0·89)	Large, randomized, controlled trial should be performed
Laupland, 2007 [70]	Adults with SI, SS or SSH	14	1450	OR = 0·66 (0·53–0·83)	Significant heterogeneity; further study needed
Kreymann, 2007 [71]	SS or SSH	27 (13 PD)	2202	0·79 (0·69–0·9)	Adjunctive use of IVIg recommended; use of IgMA-enriched IVIg preferred

BS: bacterial sepsis; CI: confidence interval; OR: odds ratio; PD: paediatric; RR: risk ratio; SE: sepsis; SI: severe infection; SS: severe sepsis; SSH: septic shock.

0·84–1·24)]. Neilson and colleagues followed with another meta-analysis, but restricted their analysis to studies evaluating immunoglobulin M and A (IgMA)-enriched preparations of IVIg in adults. They found that treatment with IgMA-enriched IVIg nearly halved the risk for death compared with control patients not treated with IVIg (Table 3).

The publication in 2006 by Hentrich *et al.* [73], of a clinical trial evaluating IgMA-enriched IVIg in 211 patients with haematological malignancies and neutropenia with sepsis syndrome or septic shock, was followed by three meta-analyses [69–71]. Turgeon *et al.* conducted a meta-analysis of 20 reports from 18 studies (one recognized and one unrecognized duplicate publication) [69,70] in 2569 adults with sepsis. Laupland and colleagues performed a meta-analysis of 14 clinical trials with 1450 patients limited to adults with severe infections (Fig. 3) [70]. Kreymann *et al.* conducted a meta-analysis of 27 studies of 2202 patients with sepsis or septic shock [71]. Thirteen of these studies were in paediatric populations and not included in other meta-analyses. Despite the differences in studies included and methodologies used, these meta-analyses show remarkable consistency in the determination of overall mortality benefit. However, the conclusions of the authors and accompanying editorials have been inconsistent [74,75]. A number of factors must be considered in the interpretation of the results of the individual studies contributing to the pooled effect size associated with IVIg therapy.

First and foremost, the methodological quality of a study has an important influence on the interpretation of effect size. The clinical trials to date conducted in adults with severe disease averaged approximately 50 subjects, and few trials have had more than 100 randomized patients [27,76]. In addition, only two-thirds reported adequate allocation concealment methods and less than half had adequate

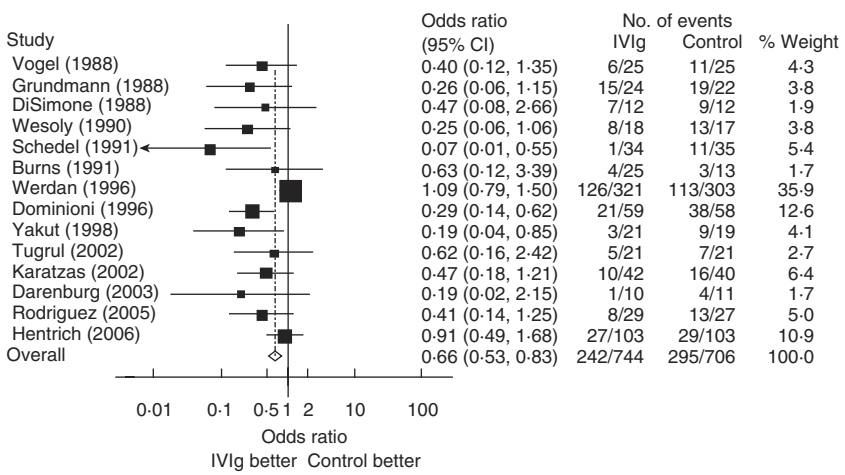

Fig. 3. Forrest plot showing the overall effect of intravenous immunoglobulin (IVIg) on mortality in adults with sepsis. CI: confidence interval. Reproduced with permission from Laupland *et al.* 2007 [70].

blinding. Recent larger, more rigorously designed trials have demonstrated much less effect of IVIg than older, smaller, less well-designed studies, raising the possibility of a treatment bias in the latter studies. It is also notable that studies using an albumin control showed less benefit than those that did not, and may reflect a potential treatment effect of albumin and adequacy of resuscitation [77]. It is also important to recognize that one carefully designed, large study (representing nearly half of all adults studied to date) showed no overall significant mortality difference with IVIg therapy, and had a major influence on the pooled effect attributable to IVIg therapy [72].

Another major consideration in the interpretation of the trials to date involves the dose and type of IVIg used. Studies that used high (> 1 g/kg body weight) doses of IVIg demonstrated greater effects. While a dose-ranging study has not been completed, the plausibility for a greater effect with higher doses (such as 2 g/kg) may be suggested based on clinical observations in other inflammatory conditions, such as Kawasaki disease [1]. The type of IVIg may have an important effect, possibly in favour of a greater pooled effect of IgMA-enriched compared with standard preparations of IVIg. IgMA-enriched preparations are associated with greater complement inactivation and improvement in microvascular perfusion in experimental models [74]. However, head-to-head clinical comparisons are limited [78]. In addition, the greater pooled effect of IgMA-enriched compared with standard IVIg is influenced by the large study by Werdan *et al.*, which found a non-significant difference in mortality with 0·9 g/kg standard IVIg (Fig. 3). Notably, the second largest clinical trial to date (211 patients) reported by Hentrich *et al.* utilized IgMA-enriched IVIg at a dose of approximately 1 g/kg and found no significant difference in mortality [73].

Despite the body of evidence supporting the use of IVIg, it has not been adopted into widespread use in the treatment of severe sepsis and septic shock. This may reflect its cost, limited supply and potential uncertainty of clinical benefit. Widely utilized guidelines have either neglected to address or not recommended its use, despite it having a stronger body of evidence and better safety profile than many other recommended therapies [57,62]. While anecdotal reports suggest that it may be used with some frequency in a number of European countries, surveys in North America indicate that it is used rarely for severe sepsis and septic shock, particularly those due to Gram-negative aetiologies [79]. However, most of the specialists surveyed reported that they would use IVIg for treatment of toxic shock syndrome, especially if it was due to invasive group A streptococcal disease associated with necrotizing fasciitis [79,80]. This practice is based largely upon theoretical rationale and anecdotal and retrospective clinical observations, as randomized clinical trials of IVIg therapy have rarely included patients with toxic shock syndrome to date.

Despite major efforts in recent years, the mortality rate remains unacceptably high for severe sepsis and septic shock in adults, and improved therapies are needed. Polyclonal IVIg is a promising adjunctive therapy for severe sepsis and septic shock in adults and pooled results of meta-analysis indicates a major mortality benefit with its use. However, due to a number of study methodological considerations and its high cost and limited supply, its use has not been recommended or adopted widely. While clinical judgement may guide its use in individual cases, further study is needed before it can be recommended routinely. An adequately powered, rigorously designed trial comparing high dose standard/IgMA-enriched IVIg *versus* albumin placebo should be undertaken with the highest priority.

While this report focuses upon the use of IVIg for adjunctive therapy in severe infections in adults, it is noteworthy that IVIg has also been used to treat infections in high-risk neonates [81]. The International Neonatal Immunotherapy Study, a large (3493 subjects) multi-centred randomized trial evaluating IVIg therapy for suspected or proven sepsis, has been closed recently to further enrolment, and results are expected to be published in 2010 [82]. Hopefully, this trial will allow a definitive recommendation surrounding the use of IVIg as an adjunctive therapy for neonatal sepsis.

Summary

The clinical use of IVIg has expanded beyond patients with immunodeficiencies into a wide range of diseases with different pathological mechanisms. In addition to a broad range of autoimmune indications, the potential benefit of IVIg for conditions such as severe sepsis and highly sensitized transplant recipients is being recognized increasingly. Increasing attention is also being turned to the use of IVIg in combination with other agents, such as immunosuppressive agents or monoclonal antibodies. Further controlled trials are required in new disease areas, including the assessment of the cost–benefit ratio and improvements in quality of life.

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